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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/555,866	11/21/2000	IVO GLYNNE GUT	147-202P	2276

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EXAMINER	
GOLDBERG, JEANINE ANNE	

ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 11/24/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/555,866	GUT ET AL.	
	Examiner	Art Unit	
	Jeanine A Goldberg	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 September 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-23* is/are pending in the application.

4a) Of the above claim(s) *23* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. This action is in response to the papers filed September 8, 2004 . Currently, claims 1-23 are pending. Claim 23 has been withdrawn as drawn to non-elected subject matter.

Election/Restrictions

2. Applicant's election without traverse of Group I, Claims 1-22 in the paper filed September 8, 2004 is acknowledged.

The requirement is still deemed proper and is therefore made FINAL.

Priority

3. This application is a 371 of PCT/EP98/07911, filed December 4, 1998 which claims priority to EPO 97121471.3, filed December 5, 1997.

Should applicant desire to obtain the benefit of foreign priority under 35 U.S.C. 119(a)-(d) prior to declaration of an interference, a translation of the foreign application should be submitted under 37 CFR 1.55 in reply to this action.

Drawings

4. The drawings are acceptable.

Information Disclosure Statement

5. The listing of references in the Search Report is not considered to be an information disclosure statement (IDS) complying with 37 CFR 1.98. 37 CFR 1.98(a)(2)

requires a legible copy of: (1) each U.S. and foreign patent; (2) each publication or that portion which caused it to be listed; (3) for each cited pending U.S. application, the application specification including claims, and any drawing of the application, or that portion of the application which caused it to be listed including any claims directed to that portion; and (4) all other information, or that portion which caused it to be listed. In addition, each IDS must include a list of all patents, publications, applications, or other information submitted for consideration by the Office (see 37 CFR 1.98(a)(1) and (b)), and MPEP § 609 subsection III. A(1) states, "the list ... must be submitted on a separate paper." Therefore, the references cited in the Search Report have not been considered. Applicant is advised that the date of submission of any item of information or any missing element(s) will be the date of submission for purposes of determining compliance with the requirements based on the time of filing the IDS, including all "statement" requirements of 37 CFR 1.97(e). See MPEP § 609 subsection III. C(1).

Claim Objections

6. Claims 7-21 are objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim 7, , 10, 13, 15, 18, 20-21. See MPEP § 608.01(n). Accordingly, the claims have been treated only to the extent that they depend on Claim 1.

Claim Rejections - 35 USC § 112- Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 1-22 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A) Claims 1-22 are indefinite over the recitation "each probe" because it is unclear what probes are being referred to. The claims required nucleic acid molecules and nucleotide base sequences. The claims do not set forth probes. It is unclear whether there is a probe separate from the nucleic acid molecules and nucleotide base sequences or whether the probes are part of one of these groups.

B) Claim 9 is indefinite over the recitation "Gene32- nucleic acids linking" because it is unclear what is Gene32. The specification teaches Gene32 is a protein binding single DNA in an unspecified way. This term appears to be arbitrary and does not appear to have any meaning established in the art or the specification. It is unclear what constitutes a Gene32 nucleic acids linking. The art teaches a T4 phage Gene32, however the art also teaches a variety of newly discovered genes which have been designated Gene32. The claim has been broadly interpreted to be any protein binding.

C) Claims 20 and 22 are indefinite over the recitation "preferably" because it is unclear whether the claim requires that the ratio of the compounds or whether the claim is merely indicating that it is permissible. Thus it is unclear whether this is a limitation of the instant claims.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

8. Claims 1-9, 15 are rejected under 35 U.S.C. 102(b) as being anticipated by Tang et al. (Nucleic Acids Research, Vol. 23, No. 16, pages 3126-3131, 1995).

Tang et al. (herein referred to as Tang) teaches a matrix-assisted laser desorption/ionization mass spectrometry of immobilized duplex DNA probes. MALDI TOF mass spectrometry was used to analyze short DNA duplex probes with one strand immobilized on solid supports. Only the non-immobilized strand could be detected. Specifically, Tang teaches that streptavidin-coated magnetic beads were used and biotinylated single-stranded DNA was added to the mixture (limitations of Claim 6, 7, 8). The supernatant containing unbound oligonucleotides was removed and beads were washed. Tang teaches contacting the beads with complementary oligonucleotides to allow hybridization (limitations of Claim 2). After annealing, the supernatant with excess ligand was removed and the beads were washed.

Tang also teaches preparation of duplex DNA on CPG beads which includes in situ using B-cyanoethyl phosphoamidite chemistry (limitations of Claim 6, 15). Tang teaches that a amino and phosphate protecting groups were found on the support (limitations of Claim 7). Tang teaches that to analyze the duplex on the beads, the beads were placed on the target probe of the mass spectrometer and matrix solution was added onto the spot and allowed to dry. The matrix solution was added onto the spot and allowed to dry (0.7M 3-HPA with 10% ammonium citrate in 50% acetonitrile) (page 3127, col. 2)(limitations of Claim 3, 4). The spectrometers used employed a nitrogen laser for MALDI (page 3128, col. 1). Tang teaches using a mixture of complementary strands which were 12, 14, 16, 18, 20 and 22mers. Another mixture comprise 24-29mers. Each of the mass spectra showed the expected results (page 3130, col. 1)(limitations of Claim 5). Tang teaches that desorption of the annealed strands complementary to the immobilized strands of duplexes opens up a new strategy for DNA sequencing. Sequencing can be carried out in parallel and increase of speed by a few orders of magnitude may be expected. The design of customized DNA chips for diagnostic detection and identification of specific DNA sequences by MALDI-TOFMS can be envisioned (col. 3130, col. 2). Thus, since Tang teaches every limitation of the instant claims, Tang anticipates the claimed invention.

9. Claims 1-22 are rejected under 35 U.S.C. 102(e) as being anticipated by Van Ness et al (US 6,027,890, February 2000).

Van Ness et al. (herein referred to as Van Ness) teaches a method of gene expression analysis which involves parallel measurement of hybridization with a spectrometry. Van Ness teaches that the method includes combining a set of first tagged members with a biological sample which may contain one or more members to permit binding. The tag is correlative with a particular first member and detectable by non-fluorescent spectrometry. The bound members are separated from the non-bound members. The tag is cleaved from the first member and detected by spectrometry to detect the binding of the first member to the second member.

Van Ness teaches that any member pairs may be detected including DNA, RNA and analogues such as PNA. Van Ness teaches nucleic acid fragments with internal modification such that the base (A, T, C, or G) has been modified to add a reactive functional group (col. 36, lines 50-55)(limitations of Claims 13-14, 18). Van Ness teaches that the biomolecules may be PNA, phosphorothioates and methylphosphonates (col. 74, lines 36-37)(limitations of Claim 19).

Van Ness teaches that more than 500 different and unique tagged molecules may be utilized within a given reaction simultaneously wherein each tag is unique for a selected nucleic acid fragment, probe or first or second member and may be separately identified (col. 3, lines 30-35).

Van Ness describes the basic structure of the invention such that a tag component is bound to a linker and then to a nucleic acid fragment (col. 5, lines 20-55). Van Ness teaches that the identification of a tag by mass spectrometry is preferable based upon its molecular mass to charge ratio (limitations of Claim 10-12). Van Ness

teaches combinatorial chemistry as a means for preparing tags. The combinatorial libraries can be used as tags for the identification of molecule of interest. Combinatorial chemistry may be defined as the systematic and repetitive, covalent connection of a set of different "building blocks" of varying structures to each other to yield a large array of diverse molecular entities (col. 29, lines 20-30)(limitations of Claim 15-17, 22).

Van Ness teaches that a method for gene expression analysis includes in a particular embodiment that DNA is covalently immobilized to the solid support (limitations of Claim 2). Van Ness teaches that the solid supports can be nylon beads, polystyrene microbeads, glass beads (col. 47, lines 23-25)(limitations of Claim 6). The solid supports are preferentially coated with an amine-polymer such as polyethylene(imine), acrylamide, amine-dendrimers (limitations of Claim 6-7). Van Ness teaches the use of avidin-biotin technology has become important and detection of specific DNA/RNA sequence by hybridization (col. 46, lines 8-15)(limitations of Claim 8-9). The solid support is then interrogated (hybridized) with one to thousands of probes which are complementary to the gene of interest. Each probe is labeled with a cleavable mass spectrometry tag. Excess or unhybridized probe is washed away and the solid support is placed in the well of a microtiter plate. Van Ness teaches that the non-specifically hybridizing nucleic acids are rinsed with a solution which includes a matrix mater appropriate for spectrometry (col. 55, lines 35-37)(limitations of Claim 3-4). Van Ness teaches that the probe oligonucleotide may be denatured from the solid supports (col. 92, lines 11-15)(limitations of Claim 5). The material is mixed with alpha-cyano-4-hydroxy cinnamic acid matrix prior to mass spectrometry analysis (col. 87, lines

10-15)(limitations of Claim 20-21). The mass spectrometry tag is cleaved from the solid support and the solid support is removed from the well of sample container and the contents of the well are measured with a mass spectrometer (col. 46-47). The appearance of specific mass spectrometer tags indicate the presence of RNA in a sample and the presence of RNA in the sample and evidence that a specific gene is expressed in a given biological sample.

Conclusion

10. No claims allowable over the art.

11. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

A) O'Donnell et al. (herein referred to as O'Donnell)(Anal. Chem. Vol. 69, pages 2438-2443, 1997) teaches a high-density, covalent attachment of DNA to silicon wafers for analysis by MALDI-TOF mass spectrometry

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jeanine Goldberg whose telephone number is (571) 272-0743. The examiner can normally be reached Monday-Friday from 7:00 a.m. to 4:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (571) 272- 0745.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

J. Goldberg

Jeanine Goldberg
Patent Examiner
November 23, 2004